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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,209	12/01/2003	Jon Elliot Adler	100337.54075D2	9839

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/724,209	ADLER, JON ELLIOT	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *186-215* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *186-215* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 4/2/2007 have been entered in full. New claims 186-215 are pending.

Applicant is notified that any outstanding rejection that is not expressly maintained in this Office action has been withdrawn. Specifically, the rejection under 35 USC 112 second paragraph regarding the word "putatively" is withdrawn in view of Applicant's persuasive arguments and upon further consideration.

Claim Objections

Claim 186, 193, 203-206 are objected to because of the following informalities: The claims utilize section references (1), (2) and (3), it is recommended that letter or other references such as "i" and "ii" be used to distinguish the sectioning of the parts of the claim from the actual numbering of the claim. Additionally 186(1) appears to be missing the word "more" after the phrase "screening one or". Claims 203-206 depend from canceled claim 185. For the purpose of examination, claims 203-206 will be assumed to be depended from claim 186. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 186-215 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for the reasons put forth previously.

New claim 186 requires that at least one bitter ligand of SEQ ID NO: 4 be known. However, no such compound is asserted to bind SEQ ID NO: 4. The specification asserts that the instant hT2R54 polypeptide (SEQ ID NO: 4) is a bitter taste receptor, however the specification does not teach which of the thousands of different and structurally unrelated compounds that can be perceived by humans as bitter can actually be used to bind the hT2R54. In the parent Application 09825882, evidence was provided that after screening a specially developed library of 15,000 potential bitter tastant compounds, the inventors eventually discovered only a single compound, nitrosaccharin, that effectively activated the hT2R61 polypeptide (SEQ ID NO: 8) see Applicant's response of 5/14/2004 in the 09825882 Application. No specific teaching is provided for the instant hT2R54 as to what might activate or bind to it and nor is there any mention of the specially developed library referred to above.

Additionally, assuming that the claims can be reworded such that receptor activity or binding need only be measured but not necessarily produced or inhibited, i.e., in screening for agonists of the receptor, the instant claims 186 are directed to a genus of variants of SEQ ID NO: 4 that are not enabled. Claims 186, 193-215 encompass a genus of polypeptide variants of the polypeptide of SEQ ID NO: 4 i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 4 or comprising only "functional fragments" of SEQ ID NO: 4 Applicant has

not provided sufficient guidance as to how to make and use the encoded polypeptides which are not at least 95% identical to the polypeptide of SEQ ID NO: 4 (see the 09825882 Application), but which still retain a desired property of the polypeptide of SEQ ID NO: 4. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 4 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 4 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 4, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 4.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310,

especially p.1306, column 2, paragraph 2). Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 4 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created. Further, claim 138(b) encompasses all polypeptides comprising an amino acid sequence of (a); this includes polypeptides with as little as two amino acids in common with (a), and differing entirely in the

rest of the sequence. It is suggested that replacing the word "an" in (a) with "the" would obviate this aspect of the rejection.

The problem of producing active variants appears especially difficult in the art of T2R receptors, to which the instant polypeptide is asserted to belong. The instant specification appears to simply suggest to the artisan that art-recognized procedures for screening GPCRs (e.g. pages 50-63) are sufficient to identify functional variants of SEQ ID NO: 4 However, Hoon *et al., Cell* 96(541-551)1999, report that "We have attempted to determine the ligand/tastant specificity of TR1 and TR2 using a variety of strategies but have been hampered by the difficulty of functionally expressing these molecules in heterologous systems" see col 1 of page 547. Further, Chandrashekar et al., Cell 100(703-711)2000 reported that they were able to record a response from only 1 of the 11 human T2R clones tested, see col 1 of page 707. Thus, the art regarding T2R receptors, as exemplified by Hoon et al., and Chandrashekar et al, recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to assay functional T2R receptors. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method.

The specification has also failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 3, e.g. no disorder or phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might now where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations. The instant specification has provided

only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method. While, it may be reasonable that the instant specification is enabling for variants that are at least 95% identical to SEQ ID NO: 4, see parent Application 09825882, the scope of the instant claims is vastly wider than such and does not appear to be supported by and adequate disclosure.

Due to the large quantity of experimentation necessary to generate the essentially infinite number of variants recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the difficulties encountered in screening T2Rs, exemplified by Hoon et al. and Chandrashekar et al., and the breadth of the claims which fail to recite adequate structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues methods that were used to de-orphan other bitter taste receptors are taught in the specification, and that to find a ligand for the instant SEQ ID NO: 4 would not be unduly burdensome and that the instant inventors have found ligands that bind to SEQ ID NO: 4. This argument has been fully considered but not deemed persuasive. The art recognizes the burdensome and unpredictable nature of finding ligands for bitter taste receptors, as exemplified by Chandrashekar et al. above. The claims require a method that is not operable as it is disclosed in the specification. Compounds that bind to SEQ ID NO: 4 are required to practice the claimed

methods yet none are disclosed. The invitation to the skilled artisan to complete the invention by trying to discover compounds that can be used does not constitute an enabling disclosure.

Claims 186-215 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed above, new claim 186 requires that at least one bitter ligand of SEQ ID NO: 4 be known. However, no such compound is asserted to bind SEQ ID NO: 4. One skilled in the art would thus understand that one would need to be in possession of a compound that binds SEQ ID NO: 4 in order to practice the invention. The specification, as filed, does not provide any such compounds, thus the skilled artisan would not recognize that Applicant was in possession of the claimed invention at the time of filing.

Additionally, the specification discloses a cDNA polynucleotide of SEQ ID NO: 3 encoding a polypeptide of SEQ ID NO: 8, yet claims 186, 193-215 encompass the use of polypeptide variants not described in the specification, e.g. mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 3, encoding a polypeptide that binds a single ligand, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide of SEQ ID NO: 3, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The specification has not provided a particular essential feature, either a functional or structural feature, that the claimed genus of polynucleotides possess. The recitation of the property of hybridization does not, alone, provide sufficient information regarding the structure of the polynucleotide variants. Further, most of these variants are expected to encode polypeptides having an amino acid sequence different than that of SEQ ID NO: 4 and thus having different structural and functional properties. Similarly, the recitation of a percent identity to SEQ ID NO: 4 provides no description of any amino acid sequence other that of SEQ ID NO: 8. The specification has not defined what particular common structural or functional properties are possessed by the claimed genus of polynucleotides. Thus one of skill in the art would appreciate that Applicant was not in possession of the claimed genus of assay methods using variants of SEQ ID NO: 4.

Applicant's arguments have been substantially addressed above. The skilled artisan would not recognize that Applicant was in possession of the required binding compounds at the time of filing, nor of the genus of functional variants 90% identical to SEQ ID NO: 4.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 9:00 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

June 7, 2007

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER